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Review Article

Impact of sleep-disordered breathing treatment on upper airway anatomy and physiology

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ABSTRACT

Sleep-disordered breathing (SDB) is a major public health problem. Various anatomic, pathophysiologic, and environmental changes contribute to SDB. The successful treatment of SDB reverses many of these abnormal processes. The present article discusses the current clinical evidence that supports the reversibility and its potential application in the management of SDB. Continuous positive airway pressure reduces angiogenesis and inflammatory edema, increases pharyngeal size, and improves surrogate markers of vascular inflammation and tongue muscle fiber types. Mandibular advancement devices lead to favorable maxillary and mandibular changes, increase pharyngeal area, and improve hypertension. Uvulopalatopharyngoplasty increases posterior airway space and pharyngeal volume, reduces nasal and oral resistance, and lowers response to high CO_2. Weight loss reduces nasopharyngeal collapsibility, critical closing pressure of the airway, apnea–hypopnea index, and improves oxygen saturations. Potential clinical benefits of these changes in the management of SDB and patient compliance with treatment are discussed.

1. Introduction

Obstructive sleep apnea (OSA) is a major public health hazard and is a chronic disease with multiple systemic complications. The prevalence in the United States is estimated to be 10% for 30–49-year-old men, 17% of 50–70-year-old men, 3% for 30–49-year-old women, and 9% of 50–70 year-old women [1]. The consequences of OSA are wide ranging, such as daytime somnolence that interferes with daily function to more severe and potentially life-threatening cardiovascular, neurocognitive, and metabolic complications [2,3].

Therapeutic options in treating OSA have been focused on correcting the mechanical and inflammatory obstruction of the airway, resulting from many anatomical, neuromuscular, and functional pathophysiologic changes. To date, continuous positive airway pressure (CPAP) treatment has the most support for being an effective long-term treatment to affect all of the aforementioned issues and reduce obstructive events. Mandibular advancement devices (MADs), also known as oral appliances (OAs), are common treatments for mild to moderate OSA. Compliance is the main issue surrounding the efficacy of either CPAP or MAD. Group cognitive behavioral therapy may increase the compliance of patients utilizing CPAP [4]. Surgical interventions such as septoplasty, turbinectomy, and uvulopalatopharyngoplasty (UPPP) have been undertaken in an attempt to correct anatomical obstruction of the airways. The risk of perioperative and postoperative complications makes noninvasive modalities more desirable. Adjunctive therapies include weight loss and bariatric surgery. Obesity may cause collapsibility and narrowing of upper airways [5]. Limited studies exist on other novel approaches including positional training, tongue protrusion therapy, and hypoglossal nerve stimulation therapy. At this time, there is inconclusive evidence to support pharmaceutical agents for the primary treatment of OSA. The task of comparing all of these modalities of treatment cannot be easily accomplished because of the variable effectiveness of each modality.

1.1. The effects of CPAP on inflammatory markers

Upper airway inflammation is one of the important intermediary processes leading to airway obstruction. In patients with severe OSA, the surrogate markers of inflammation (interleukin-6 or IL-6) and of oxidative stress (8-isoprostane) are high in the exhaled breath. Tumor necrosis factor-alpha (TNF-α), high-sensitivity

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C-reactive protein (hsCRP), adhesion molecules, and monocyte chemoattractant protein-1 are high in OSA patients [6–8].

In patients with moderate to severe OSA, the levels of exhaled nasal and oral pentane and nitrous oxide significantly increased after sleep. Pentane is the product of polyunsaturated membrane fatty acid peroxidation by reactive oxygen species (ROS) that induce tissue damage by their effects on the membrane lipids and proteins [9,10].

Increased levels of adenosine and urinary uric acid in OSA patients are implicated with increased production of ROS. This strong association was recently confirmed in a large population from Sao Paulo, Brazil; concluding that an increase in 1 mg/dL in uric acid level was associated with 16% increased risk of OSA (95% C.I. = 1.01–1.33) [11]. Redox-sensitive gene expression is suggested by increase in the protein products like vascular endothelial growth factor (VEGF), erythropoietin, endothilin-1, inflammatory cytokines, and adhesion molecules [12,13].

Treatment of OSA has been shown to change the levels of inflammatory markers favorably [14]. The physiologic and biologic changes mentioned above lead to multisystem complications when the degree of injury outweighs the compensatory mechanisms. The treatment of OSA with CPAP is indeed associated with the reversal of the many biologic abnormalities [15–24].

In one study, CRP and IL-6 levels were higher in patients with OSA compared with obese control subjects (CRP $P < 0.001$, IL-6 $P < 0.05$), confirming the role of inflammatory responses in the development of atherosclerosis and coronary artery disease. CRP induces adhesion molecules on the endothelial cells and chemokine production, while IL-6 plasma level is correlated with mortality rate in patients with coronary artery disease and the risk of developing a myocardial infarction in healthy men. Both CRP and IL-6 levels improved after treatment with CPAP [25–27]. Drager et al. documented the sustained changes that occurred in the histopathology of the vascular system because of OSA and reversal that could be attributed to CPAP treatment. Significant improvement occurred after a treatment period of 4 months with CPAP in patients with severe OSA. The carotid artery intima-media thickness (707 ± 105 μm vs. control group 645 ± 95 μm, $P = 0.04$) and arterial stiffness were measured as pulse wave velocity (10.4 ± 1.0 m/s vs. 9.3 ± 0.9 m/s, $P < 0.001$) between baseline and follow-up. Posttreatment improvement in carotid intima-media thickness ($P < 0.05$) and pulse wave velocity (<0.01) supports the concept that OSA is an independent risk factor for atherosclerosis [28].

In a study by Mansour et al., 6 weeks of therapy with CPAP significantly decreased the levels of CRP, IL-6, and TNF-α in patients with moderate to severe OSA. IL-6 levels before (3.13 ± 0.56) and after CPAP (1.87 ± 0.15, $P < 0.0001$), TNF-α before (7.4 ± 1.29) and after CPAP (4.77 ± 0.96 $P < 0.0001$), and CRP before (0.83 ± 0.1) and after CPAP (0.44 ± 0.18 $P < 0.0001$) were noted [29].

Nural et al. demonstrated that levels of CRP decreased significantly in both the OSA and overlap syndrome patients (patients with OSA and chronic obstructive pulmonary syndrome) who were treated with CPAP for 3–6 weeks. However, in this study, levels of TNF-α and asymmetric dimethylarginine (ADMA) in OSA and overlap syndrome groups did not decrease significantly after treatment with CPAP [30]. A study by Ryan et al. demonstrated no effect on CRP levels after treatment with CPAP (2.29 (1.32–4.10) vs. 2.84 (1.13–5.40) mg/l; $P = 0.145$) [31]. Similarly, a randomized controlled trial by Kohler also documented no decrease in CRP levels with a difference between median changes −0.24 mg/l (95% confidence interval (CI) −0.88 to +0.24); $P = 0.30$) [32].

Although this topic may appear to be controversial, meta-analysis of 10 peer-reviewed studies showed that CRP levels were demonstrated to be reduced (mean decrease of 17.8%, $P = 0.002$) by CPAP treatment. According to the authors, recent studies suggest that CRP elevation in patients with OSA may be independent of obesity [33].

In addition, the level of 8-isoprostane, a marker of lipid peroxidation, which is elevated in OSA patients, reduced after 12 weeks of CPAP treatment (mean 38.5 pg/ml at baseline vs. 22.5 pg/ml on CPAP, $P = 0.0001$) and levels of nitrates, which were decreased in OSA patients, improved (mean 280 μmol/l at baseline vs. 1373 μmol/l post-treatment, $P = 0.0001$) [34].

It has been suggested throughout the reviewed literature that treatment with CPAP for 3–6 months is adequate to document changes in inflammatory marker levels. Many reviewed studies followed a shorter interval, were not controlled, and did not incorporate the confounding effects of smoking history and previous lung or cardiovascular disease [33].

1.2. CPAP treatment and ROS

In OSA, release of ROS from neutrophils in response to hypoxia leads to inflammatory cascades that cause endothelial damage. Neutrophil-reactivated oxygen species has been demonstrated to be correlated with degree of severity of OSA and was found to be independent of obesity [35]. In a prospective case series by Steiropoulos et al., the effect of CPAP on surrogate markers of inflammation was studied. In patients with OSA, the baseline levels of lymphocytes, serum TNF-α, IL-6, and uric acid levels were measured. Repeat levels were obtained after 6 months of treatment with CPAP in one group and from a control group without any intervention. A significant decrease in levels of TNF-α and uric acid levels was noted in the CPAP-compliant (>4 h/night) group. TNF-α levels decreased by a mean of 8.41 ± 5.7 pg/ml vs. baseline 5.72 ± 4.91 pg/ml, $P = 0.001$. Uric acid levels decreased by a mean of 8.79 ± 1.48 mg/dl vs. baseline 6.2 ± 1.37 mg/dl, $P < 0.001$. However, IL-6 levels showed no significant change (2.71 ± 1.27 pg/ml vs. baseline 2.46 ± 1.08 pg/ml, $P = 0.266$) [36].

A controlled study by Barceló et al. in 2006, suggests that CPAP use may ameliorate oxidative stress. Plasma total antioxidant status (TAS), activity of antioxidant enzymes, glutathione peroxidase (GPX) and γ-glutamyl transferase (GGT), antioxidant vitamins (A, E, B_{12}, and folate), and homocysteine levels were compared before and after CPAP treatment. Patients with OSA had lower baseline TAS (1.4 ± 0.16 vs. 1.50 ± 0.10 mmol l^{-1}), vitamin A (64 ± 19 vs. 74 ± 17 μg dl^{-1}) and vitamin E levels (1,525 ± 499 vs. 1,774 ± 503 μg dl^{-1}), and increased values of GGT (42 ± 22 vs. 32 ± 16 U l^{-1}) than controls. There was no difference between groups in GPX, homocysteine, vitamin B_{12}, and folate plasma levels. In the group with OSA, CPAP treatment normalized levels of TAS (1.50 ± 0.13 mmol l^{-1}) and GGT (30 ± 14 U l^{-1}) without effect on vitamin levels [37].

A controlled prospective study by Jelic et al. also suggests that CPAP therapy is associated with the reversal of oxidative stress. In patients with OSA, expression of endothelial nitric oxide synthetase (eNOS) (mean 0.19 at baseline to 0.77 at follow-up) and phosphorylated eNOS increased (from 0.0 to 0.28 at follow-up), whereas expression of nitrotyrosine (1.64–0.35), cyclooxygenase-2 (1.36–0.16), and inducible NOS (0.44–0.20) significantly decreased in patients who adhered to CPAP ⩾ 4 h daily [38].

1.3. Role of CPAP in changing levels of VEGF

Angiogenesis is a known adaptive response to tissue hypoxia [39]. Formation of new blood vessels increases the blood supply to ischemic tissue in an effort to compensate for the decrease in oxygen concentration. VEGF, a key mediator of angiogenesis, is a cytokine that regulates many functions of the vascular endothelial cell. It is upregulated by hypoxic stimulation in cardiac myocytes, vascular smooth muscle cells, and the endothelial cells. VEGF may

independently contribute to atherogenesis in OSA patients [40–43].

OSA patients have high concentration of serum VEGF that correlates with the severity of the OSA and the apnea–hypopnea index (AHI) [44]. From a series of experiments, Lavie et al. suggested a positive correlation between AHI and VEGF levels (129.1 ± 43.4 pg/ml in OSA patients vs. 32.5 ± 12.8 pg/ml in non-OSA patients $P < 0.007$) and a remarkable decrease in VEGF concentration (57.1 ± 62.5 pg/ml before CPAP treatment vs. 39.6 ± 46.9 pg/ml after CPAP treatment, $P < 0.01$) [45]. Three recent studies indicated that VEGF may be unrelated to oxidative stress and may be influenced by OSA-related factors like hypertension, body weight, and age [46,22,47].

1.4. The effects of CPAP on the sympathetic nervous system

Significant increase in sympathetic activity is present in OSA patients due to tonic activation of chemoreflex activity. This, along with chronic intermittent hypoxia, leads to up-regulation of the renin–angiotensin system and down-regulation of nitric oxide synthesis. Cyclic intermittent hypoxemia-induced chemo-excitation may occur by augmentation of the peripheral chemoreflex sensitivity and by direct effects on sites of central sympathetic regulation [48].

Increased sympathetic and decreased parasympathetic modulations are well described in patients with even mild forms of OSA. Reduced heart rate variability (HRV) is a newer marker for OSA. Balchandran et al. studied 74 subjects with OSA. Electrographic R–R interval in milliseconds vs. time in seconds and Fourier transforms (amplitude in milliseconds vs. time in seconds) were plotted for OSA patients and controls. Compared to controls, many daytime time- and frequency-domain metrics of HRV including low-frequency and high-frequency power (parasympathetic modulation) were reduced in OSA [49].

CPAP has been demonstrated to reduce sympathetic nerve activity. Maser et al. followed up 29 OSA patients before and after treatment with CPAP for 6 weeks to monitor cardiovascular autonomic nerve fiber function. Reduced heart rate variation is the earliest indication of cardiovascular autonomic dysfunction. R–R interval variation during deep breathing was measured by vector analysis. CPAP improved the cardiovascular autonomic function as assessed by mean circular resultant (MCR) and expiratory to inspiratory ratio to incorporate effect of breathing on R–R intervals. Resting supine diastolic blood pressure (DBP) and mean arterial pressure (MAP) also improved on CPAP [50]. The sensitivity of the baroreflex is reduced during sleep and wakefulness in OSA patients. CPAP increased baroreceptor sensitivity to heart rate in patients with severe OSA [51]. In another study, 102 OSA patients were monitored for 4 weeks of CPAP therapy. Significant reductions in urine normetanephrine excretion (from 179 ± 80.1 to 132.7 ± 46.5) improved baroreflex sensitivity (from 7.1 to 8.8 ms mm Hg^{-1}) and reduced arterial blood pressure by 2.6 mmHg [52]. In a recent study, CPAP therapy was withdrawn to assess the effect on the surrogate markers of the sympathetic activity and the vascular inflammation. An immediate return of OSA and a progressive increase in AHI was observed after one and seven nights without CPAP, respectively. High levels of urinary noradrenalin, as a marker of increased sympathetic activity, were present after seven nights without CPAP. This finding positively correlated with the degree of nocturnal hypoxemia [53].

1.5. Effects of CPAP on oropharyngeal anatomy and pharyngeal size

There has been significant interest in studying the effect of CPAP on pharyngeal size and OSA. Studies have suggested that in patients with OSA, CPAP is able to reverse many anatomical changes caused by years of inflammation. These studies can be classified as the ones that describe changes in anatomy and physiology while CPAP is in active use by the subject and others that evaluate lasting changes that are measurable when CPAP is removed. Such observations suggest possible reversibility of the inflammatory processes, decrease in pharyngeal edema, improvement in sleep fragmentation, and increased upper airway muscle tone. Mortimore et al. demonstrated that long-term CPAP use increased upper airway caliber in OSA. The magnitude of the upper airway volume increase correlated with average CPAP use time at night. Posterior airway space (PAS) was measured by lateral cephalometry before initiation and 3 months after initiation of CPAP therapy. PAS in supine position increased with CPAP from a mean of 11.8 ± 0.8 mm to 13.4 ± 0.8 mm, but not in the erect position [54]. This could be explained by the gravity dependence of the edema. Another possible mechanism is improvement in the function of the pharyngeal dilator muscles [55]. Improved mucosal edema due to CPAP use increased reflex palatal activity in response to negative pressure. Sleep deprivation appears to increase the severity of OSA. Improvement in sleep quality with less sleep fragmentation is known to improve the upper airway muscle activity. Leiter et al. demonstrated that sleep deprivation selectively decreased genioglossus electromyogram (EMG) activity during carbon dioxide rebreathing in awake older subjects. They suggested that this influence of sleep deprivation may play a role in the pathogenesis or severity of OSA [56].

Corda et al. evaluated the changes in short-term and long-term treatment with CPAP in 10 obese patients with OSA. Using acoustic pharyngometry, various oropharyngeal area measurements were taken. In addition, expired air volume was measured in the first 0.5 s after the application of −5 cm H_2O negative expiratory pressure (V1 NEP 0.5) at the mouth during wakefulness in the supine position at baseline, after 1 week and 6 months of CPAP therapy. The effects in cross-sectional area in both oropharyngeal and pharyngeal space incrementally increased over time. A corresponding increase in the expired air volume was noted. This study successfully concluded that the local effect of CPAP in OSA is confined not only to temporary upper airway dilation by its mechanical action but also to anatomical and functional improvement even during wakefulness. CPAP caused an early improvement in the anatomical aspect and a delayed effect on the functional aspect of the airway [57].

The role of the genioglossus muscle in airway obstruction is important. The genioglossus muscle acts as a hydrostat in order to apply force in multiple directions. It functions as an important pharyngeal dilator muscle. The muscle tone in the genioglossus is increased in patients with OSA during sleep and in wakefulness. A primary myopathy may change its function leading to increased pharyngeal collapsibility. Similarly, vigorous contractions of the tongue, while ending the obstruction in patients with OSA, may cause muscle injury and repair that contribute to pharyngeal collapsibility. Tongue biopsies exhibited increase in type II muscle fibers with resultant enhanced fatigability and less endurance that improved after CPAP use. The reversal of the fiber types to type I fibers and other favorable changes occurred after 1 year of treatment with CPAP [58].

2. Effect of the MADs in the treatment of OSA

2.1. Changes in occlusal and dental structures

In a 2006 study, Ribeiro de Almeida et al. presented their findings of changes in occlusal and dental structures in patients who had been using MAD for >5 years. The use of MAD induced favorable occlusal changes (advancement of the mandible) in 41.4% of

the patients, unfavorable changes in 44.3%, while 14.3% of the patients had no change. The observed changes were dependent on the craniofacial characteristics of the patient. While the maxilla was more stable, the mandible had significant changes in arch length and inter-canine and inter-molar distances [59].

Rose et al. followed up OSA patients using MAD for over 2 years. Subjectively, minor unfavorable alterations in the mandibular occlusion were reported. The anteroposterior position of the molars and the inclination of the incisors changed favorably reducing overjet and overbite without any statistically significant change in the mandibular position [60].

Interesting observations were made in a study by Fransson et al. who evaluated the changes in the airway passages and dentofacial features in patients who used MAD for over a period of 2 years. In 65 patients, the authors noted increased linear distance in the pharynx compared to the baseline, almost 9% increase in the pharyngeal area and decrease in the velum area (mean -31.5 mm^2 [2], accounting for 50% of the increase in the relative area of the pharynx). Mandibular protrusion was slightly reduced (average $-0.4°$ ($P < 0.01$)), while lower incisors proclined on an average $+1.5°$ [61].

In a prospective study, the orthodontic changes were followed for a period of over 2.5 years while using MAD for OSA. Compared with the controls, the treatment group showed significant reduction in overjet and overbite [62]. Similar findings were noted by cephalometric analysis, including decrease in the mean upper incisor to maxillary angle from $102 \pm 2°$ at baseline to $101 \pm 2°$ after 12–30 months ($P < 0.05$). Reductions in both overjet and overbite (mean reduction <1 mm) were present during an observation period of 2.5 years [63].

2.2. MAD use and change in anteroposterior dimensions of upper airways

MAD is known to increase the anteroposterior dimensions of the oropharyngeal part of the upper airway. These improvements also occur in the lateral dimensions. Dental and skeletal changes were reported in lower face height, vertical condyle position, incisor angulation, overbite, and overjet. These changes develop over a period of many months [64]. Many of the above-mentioned studies strongly suggest that the use of MAD is responsible for certain favorable and measurable changes that occur over time.

2.3. The effects of OAs on blood pressure

Meta-analysis of seven randomized controlled studies demonstrated pooled data for mean daytime changes in systolic blood pressure (SBP), DBP, and MAP as -2.7, -2.7, and -2.40 mmHg, respectively, after using an OA [65]. Reduction in blood pressure using CPAP is similar according to a meta-analysis of 32 studies, demonstrating a diurnal SBP and DBP reduction of -2.58 and -2.01 mmHg, respectively [66]. The results of these studies may be confounded by concomitant use of blood pressure medications and mostly contained small numbers of overweight male participants of middle age.

2.4. The effects of MAD usage on oxidative stress and endothelial dysfunction

OSA-related oxidative stress and endothelial dysfunction also improve with the use of MAD [67,68]. Itzhaki et al. assessed endothelial function by reactive hyperemia–peripheral arterial tonometry (RH–PAT), a device consisting of two finger-mounted probes that measured pulse wave amplitude. Endothelial function was reported as being improved from an RH–PAT index score of 1.77 ± 0.4 at baseline to 2.08 ± 0.5 at the 3-month evaluation and 2.0 ± 0.35 at the 1-year evaluation ($P = 0.028$ and 0.055, respectively). In this study, a measure of lipid peroxidation, thiobarbituric acid-reactive substance (TBARS) levels improved with a reported decrease from 18.8 ± 6.2 nmol malondialdehyde (MDA)/ml before treatment to 15.8 ± 3.9 MDA/ml after 3 months of treatment ($P = 0.09$) and 15.5 ± 3.2 nmol MDA/ml after 1 year of treatment ($P < 0.05$). There was a correlation between the improvement in AHI and in endothelial function and TBARS levels ($r = 0.55$; $P = 0.05$).

3. Effects of surgical intervention

Over the years, many surgical interventions have developed for the treatment of OSA including phase I nasal surgical procedures like septoplasty and turbinectomy and palatal procedures like UPPP. More complex and invasive phase II procedures like genioglossus advancement and hyoid bone suspension and mandibular and maxillary advancement (MMA) tend to have better success rates. Tracheostomy, the highest-level invasive procedure for OSA, however, has multiple potential complications and side effects. Post-obstructive pulmonary edema may be more common following tracheostomy in OSA patients, and granulation tissue formation may lead to obstruction of airways [69]. The success rate seems to correlate with a higher level of surgical intervention.

UPPP is arguably the most prevalent procedure that has unpredictable results. Introduced by Fujita in 1981, the uvula and part of the soft palate are removed during UPPP to increase pharyngeal airspace. Many studies have addressed an important aspect of UPPP surgery on voice quality and nasal resonance. In one such study by Abu El-ella et al., patients were instructed to produce a standardized oral sentence and a nasal sentence. An acoustic analysis of speech (nasometry) was done to analyze pre- and postoperative nasality changes. No statistically significant differences were found between pre- and postoperative measurements in patients who underwent either UPPP or laser-assisted uvulopharyngoplasty (LAUP) in nasalance of oral sentence and nasal sentence [70].

The upper airway changes that lead to an improvement in OSA symptoms have been reviewed in many objective studies that focused on the anatomical changes at the oropharyngeal level. In a retrospective case study in 1998 by Langin et al., cephalometric measurements of the PAS were made by pharyngeal computed tomography (CT). The length, width of the soft palate, and distance between the hyoid bone and mandibular plane were recorded. In addition, the cross-sectional area at the oropharyngeal level was measured. These findings were compared between the responders and non-responders. After UPPP, there was a decrease in the length (40 ± 6 vs. 29 ± 5 mm, $P < 0.0006$) and an increase in the width of the soft palate (11.5 ± 2.7 vs. 13.6 ± 3.5 mm, $P \leqslant 0.006$). The increase in the cross-sectional area correlated with the linear reduction in AHI ($r = -0.54$, $P < 0.02$). The authors concluded that the results of UPPP were mediocre with seven responders (35%) and 13 non-responders (65%) using polysomnographic (PSG) criteria. There was no significant change noted in the hypopharyngeal area [71].

Using the upper airway critical pressure (Pcrit) that determines at what point the airway would collapse when negative pressure is applied before and after the UPPP in patients with OSA, Schwartz et al. demonstrated a significant decrease in sleep-disordered breathing (SDB) rate during non-rapid eye movement (REM) sleep and a corresponding reduction in the Pcrit. While the Pcrit values were similar in both the responders and non-responders to UPPP, the strength of the linear relationship exclusively favored responders [72].

Decreases in nasal and pharyngeal resistance because of UPPP may reduce apneic events in OSA. In a study by Kawano et al., the physiologic reduction in the nasal and oral resistance was

measured before and after UPPP, using microrhinograph and magnetic resonance imaging (MRI) scan. Nasal and oral respiratory resistance significantly decreased postoperatively ($P < 0.05$) [73].

3.1. Effects of UPPP on pharyngeal area volume

In a 1989 study, pharyngeal area volume positively correlated with improvement in snoring or OSA based on UPPP-related postoperative changes in the functional residual capacity (FRC) and the residual lung volume (RV). The authors calculated the lung volume dependence of the pharyngeal area defined as the percent change between FRC and RV, normalized to the area at FRC. This parameter represented the pharyngeal collapsibility. After the UPPP, the pharynx became stiffer, less collapsible, and less dependent on the lung volume [74].

An increase in the retropalatal surface area (RPSA) after UPPP is recently demonstrated using fiber-optic nasopharyngoscopy in a study by Tanyeri et al. Retropalatal area photographs at the base of the uvula were compared pre- and postoperatively. The retropalatal area increased from $63.39 \pm 29.3\ mm^2$ to $143.82 \pm 57.8\ mm^2$ after UPPP. These findings correlated with a mean respiratory disturbance index (RDI) decrease from 22.95 ± 19.2 events/h to 9.0 ± 8.2 events/h ($P = 0.011$) [75].

3.2. Effects of UPPP on hypercapnic ventilatory response

An increased ventilatory response to hypercapnia is found in OSA patients. After UPPP, a lower hypercapnic ventilatory response (HCVR) has been demonstrated in a study by Suzuki et al. In this study of 11 patients with OSA, the average of the hypercapnic ventilatory response (HCVR) slope was 1.93 ± 0.20 l/min/mmHg preoperatively and 1.78 ± 0.222 l/min/mmHg postoperatively. There were no significant differences before and after treatment, although OSA improved postoperatively. In the control group, the HCVR slope showed no significant difference before and after the procedure. When UPPP responders were compared to non-responders, there was a significant difference between the average HCVR slope of responders (1.59 ± 0.21 l/min/mmHg) and that of non-responders (2.52 ± 0.20 l/min/mmHg). There was no significant difference between the treatment group and non-treatment group in age, body mass index (BMI) and one-piece tonsil weight, blood gas values, cephalometric, spirometric, or sleep parameters [76].

Boot et al. reviewed long-term effect of UPPP and documented that the response to UPPP for OSA decreases progressively over the years after the surgery. Overall snoring and excessive daytime sleepiness increased slightly between 6 months and long-term follow-up. The improvement of oxygen desaturation index (ODI) decreased between 6 months and long-term follow-up ($P < 0.03$) [77] in a 4-year follow-up of treatment with MAD or UPPP in OSA patients. The success rate in the MAD group was 81% versus UPPP group 52% ($P < 0.05$). Normalization of AHI was noted in 63% of the MAD group and 33% of the UPPP group ($P < 0.05$) [78].

3.3. UPPP plus mandibular osteotomy with genioglossus advancement

Studies addressing more complex multilevel surgical interventions are few. According to a recent publication, multiple PSG parameters, validated scale of sleepiness, and markers of OSA severity (like AHI and ODI) improved following UPPP plus mandibular osteotomy with genioglossus advancement in 20 patients with various severities of OSA. Preoperatively, cephalometric analysis showed long and thick soft palate, narrow posterior air space in retroglossal area, mild mandibular and maxillary deficiency, and lowered position of the hyoid bone. Postoperative PSG (6 months after surgery) showed significant improvement in the sleep architecture. The mean AHI ± standard deviation (SD) decreased from 60.5 ± 16.5 to 44.6 ± 27 ($P = 0.007$) and CT90 (percentage of time with oxyhemoglobin saturation below 90%) decreased from $39.5 \pm 26\%$ to $25.1 \pm 26.4\%$ ($P = 0.002$). Overall success of UPPP plus mandibular osteotomy with genioglossus and hyoid advancement procedure varied depending on the severity of the OSA. In the patients with severe OSA, the success rate (AHI < 20) 6 months post surgery and subjective clinical improvement) was only 9%, 57% in moderate OSA (AHI 41–60), and 100% in mild OSA (AHI 21–40) [79].

3.4. A meta-analysis of various surgical interventions for OSA

In a recent meta-analysis, Caples et al. reviewed multiple studies addressing various currently applied surgical interventions for the treatment of OSA. Evaluation of nine case series on MMA demonstrated a reduction from a baseline mean AHI of 54.4/h to a postoperative mean AHI of 7.7/h (87.7% decrease). Risks of this surgery include possible dental malocclusion and facial neurosensory deficits. Common criteria in selecting patients for MMA include hypopharyngeal and/or velo-oropharyngeal narrowing (commonly associated with skeletal hypoplasia and micrognathia).

Meta-analysis of 15 UPPP studies revealed a reduction from a baseline mean AHI of 40.3/h to a postoperative mean of 29.8/h (33% decrease). Similar results are reported for two randomized controlled trials for LAUP, a decrease from a baseline mean of 18.6–14.7/h post surgery (32% decrease). However, the authors cautioned that most of the data are drawn from small case series and variable surgical approaches. Sleep study methodologies were often not standardized. There is a need for further trials focusing on the standardization of preoperative approach and surgical targets [80].

4. Effects of weight loss on OSA

Approximately 70% of patients suffering with OSA are overweight or obese. The severity of OSA correlates with weight gain. By virtue of its effect on the upper airway structure and function, respiratory drive and load compensation, obesity reversal should be expected to have measureable changes on many of these parameters. Using the Wisconsin Sleep Cohort Study data, in a longitudinal follow-up period of 11 years, Peppard et al. documented a 10% weight gain predicted a sixfold increase in the odds of developing moderate to severe OSA and a 32% increase in AHI. In addition, a 10% weight loss predicted 25% decrease in AHI [81].

Meta-analysis by Anandam et al. of 10 articles with a patient pool of 433 demonstrated that dietary weight loss could be useful in reducing the AHI in patients with OSA. A pooled mean BMI reduction of $4.99\ kg/m^2$ (95% CI 4.0–5.9) was noted. The pooled pre-intervention mean AHI was 50.9 events/h of sleep. After weight loss, it decreased to 27.4 events/h ($P < 0.001$). Compared to control, the weighted mean difference of AHI was decreased by −16.24 events/h (95% CI −24.4 to −8.0; $P < 0.001$) in favor of the dietary weight loss [82].

4.1. Dietary weight loss and decreases in pharyngeal collapsibility

It has been accepted for a long time that dietary weight loss has an effect on breathing and it decreases pharyngeal collapsibility. In 1987, a study by Suratt et al. reported that a weight loss of 13% decreased nasopharyngeal airway collapsibility, AHI, movement arousals, and improved PO_2 and PCO_2. This study did not report quantitative data [83]. Rubinstein and colleagues reported improvement in pharyngeal and glottic function and found a correlation between weight loss and a reduction in AHI. These findings

are reported to correlate with predictable improvement in AHI, pharyngeal patency, and reduced total oxygen consumption (VO_2) and carbon dioxide production (VCO_2). Reduction in the lateral subcutaneous neck fat width was reported in the MRI scan. Pulmonary function tests in this study revealed that both FRC and forced expiratory volume in 1 s (FEV_1) increased [84].

Considering the fact that weight gain increases the upper airway collapsibility, Schwartz et al. evaluated the effect of weight loss on the upper airway collapsibility by measuring the Pcrit before and after a 17.4% reduction in BMI. Their findings were consistent with a significant decrease in non-REM sleep OSA events and Pcrit. The decrease in Pcrit was associated with resolution of OSA when Pcrit dropped below −4 cm H_2O [85].

4.2. Dietary weight loss and an increase in the baroreflex sensitivity

The effects of a very low calorie diet were prospectively examined in 15 obese patients with OSA. There was a significant improvement in the ODI during sleep (31 ± 20 to 19 ± 18, $P < 0.001$). Weight loss produced an increase in the baroreflex sensitivity, reporting a 49% mean increase in sensitivity after weight loss. This may be protective to cardiovascular complications of OSA and may have prognostic value [86].

4.3. Pharmaceutical weight reduction

Pharmaceutical weight reduction agents are sometimes used in the management of OSA. Sibutramine seems to be a common medication used in weight loss studies. In one open uncontrolled cohort study, 87 obese men with OSA were treated with Sibutramine. At the end of the 6-month interval, subjects had lost approximately 10% of their initial body weight. Reduction in neck and waist size was accompanied by reduction in respiratory distress index (RDI), which fell by 16.3 ± 19.4 events/h and the Epworth score by 4.5 ± 4.6, both $P < 0.0001$ [87]. Another recent study compared the Sibutramine-induced weight loss to the utilization of CPAP. Sibutramine was given to the 22 obese subjects with OSA for a period of 1 year. Although many parameters were compared, only nocturnal oxygen saturations improved after weight loss [88]. In a 6-month open-label weight loss trial, authors evaluated obese subjects with OSA, combining Sibutramine and a 600-kcal diet. Markers of metabolic function, cardiovascular function, and CT-quantified intra-abdominal and liver fat were assessed. Reduction in the visceral and subcutaneous abdominal fat and liver fat was noted. All other monitored parameters like insulin resistance, high-density cholesterol (HDL), and total cholesterol to HDL ratio improved. In addition to the reduction in the liver fat, a positive association between the improvement in hypoxemia and insulin resistance was noted [89].

Another recent study described the use of phentermine plus extended-release topiramate to induce weight loss and reported improvements in RDI, AHI, mean overnight oxygen saturation, and SBP. Winslow et al. conducted a randomized, double-blind, placebo-controlled trial over a 28-week treatment period in patients with a BMI of 30–40 kg/m^2. At week 28, there was a mean decrease in weight of 10.2% in the phentermine 15 mg plus extended-release topiramate 92 mg group compared with only 4.3% in the placebo group ($P = 0.0006$) and a positive correlation ($P = 0.0003$) between percent change in weight and change in AHI. In the test group, mean AHI decreased from a baseline of 44.2 to 14 events/h at 28 weeks compared with the control group (mean AHI 45.2 events/h decreased to 27 events/h at 28 weeks). More subjects in the phentermine 15 mg plus extended-release topiramate 92 mg group with a severe AHI (>45) at baseline, achieved an AHI < 5 by week 28 than those receiving placebo (23.8% vs. 0%, respectively). This suggests that even a moderate weight loss in obese patients can lead to an improvement in AHI. However, phentermine, a stimulant, increased heart rate in the test group (least-squares mean heart rate increase of 7.7 bpm in test vs. placebo 1.7 bpm). Even a modest weight loss in the test group improved blood pressure significantly (mean decrease −15.0 mmHg systolic, −6.3 mmHg diastolic vs. −7.3 mmHg systolic and −5.6 mmHg diastolic in placebo group) [90].

4.4. Surgical weight reduction

Surgical weight reduction is a reasonable option available to morbidly obese (BMI > 40) individuals who have failed other methods of weight loss. Charuzi and colleagues followed 51 morbidly obese subjects with OSA for 8 years after they underwent Roux-en-Y gastric bypass and the vertical banded gastroplasty. Mean apnea index improved remarkably, and almost 75% of the subjects had an AHI < 10 events/h. Sleep architecture and stages improved postoperatively. In a long term, 7-year follow-up, almost 65% subjects had regained their body weight and had recurrence of OSA [91].

Proximal gastric bypass was done in 110 patients with OSA in a prospective study. Almost 50% of the subjects were followed up for 5–7 years. Significant improvement in AHI was noted in two-thirds of the patients. Interestingly, no significant weight regain was noted in this cohort [92].

The mechanisms responsible for improvement in severity of OSA by weight loss have been explored in a number of studies. Weight loss causes a reduction of nasopharyngeal collapsibility and resistance implying that the caliber of the upper airway increases. Busetto et al. used acoustic pharyngometry to measure pharyngeal cross-sectional area. At baseline, pharyngeal cross-sectional area was significantly reduced in obese individuals with OSA compared to non-obese controls. Six months after intragastric balloon insertion, weight loss was associated with significant increases in cross-sectional area at the oropharyngeal junction in both upright and supine positions. However, mean pharyngeal cross-sectional area at the glottis level was still significantly lower than for non-obese controls [93].

One study using CT imaging in OSA patients showed that velopharyngeal volume and lateral diameter increased while facial and abdominal fat volumes decreased along with parapharyngeal fat pad volume. In this study, reduction in upper airway length and the visceral abdominal fat best explained the improvement in AHI after weight loss. The changes in parapharyngeal fat did not correlate with changes in AHI [94].

A reduction in central adiposity and resultant reduction in production of adipokines that act on the central nervous system may lead to enhanced neuromuscular control of pharyngeal caliber [95]. Weight loss is associated with improvement in vital capacity, total long volume, FRC, and FEV, and this increase in lung volume may result in increased tracheal traction on the pharynx and therefore reduced pharyngeal collapsibility [96]. Impact of surgically induced weight loss on OSA was evaluated by Valencia et al. OSA was eliminated in 46% of obese patients. Although neck, thorax, waist, and hip circumference decreased, only neck circumference correlated with AHI ($P < 0.0001$) [97]. In a case series of 1–12 years follow-up to evaluate the long-term outcomes of bariatric surgery on respiratory disturbance index (RDI), Scheuller et al. reported reduction in RDI by 55% (preoperative RDI 96.9 vs. postoperative RDI 11.3) and improvement in oxygen saturation from preoperative value of 58.7% to postoperative value of 85.2% [98].

4.5. CPAP therapy and weight loss

In a retrospective study, Redenius et al. reported weight gain in CPAP-compliant users compared to controls ($P = 0.0443$) at 1-year

observation point. They suggested that development of resistance is related to the satiety-regulating hormone, leptin. Average initial BMI of CPAP subjects was 35.9 ± 10 kg/m^2 and of control subjects was 33.5 ± 7.8 kg/m^2. In the CPAP group, 53.0% of subjects gained or lost >1 kg/m^2. In the control group, 55.6% of subjects gained or lost >1 kg/m^2. The change in BMI between CPAP and control subjects did not significantly differ after 1 year ($P = 0.3157$). Women in the CPAP group gained significant weight with respect to their own initial BMIs ($P = 0.0319$). No difference was found between the initial and final BMI in control women ($P = 0.7751$). This study underscored the need for a larger, prospective study [5].

Weight loss may be complimentary to OSA treatment. Weight loss tends to improve various parameters of OSA, most notably AHI. The degree of improvement, however, remains variable. OSA recurrence has been reported despite the lack of weight regain. Pillar et al. reported increase in apnea index from 11 ± 16.4 to 24 ± 23 events/h ($P < 0.05$), while BMI increased only slightly from a preoperative value of 33 ± 7.5 kg/m^2 to a postoperative value of 35 ± 6.0 kg/m^2 ($P > 0.2$) over a 7.5-year period [99]. Long-term maintenance of therapeutic efficacy of the weight loss was assessed by Sampol and colleagues in 216 overweight patients. This study reported a lack of correlation between changes in AHI and BMI ($P < 0.156$) and demonstrated intra-individual variability [100].

5. Clinical significance

Poor compliance with CPAP has generated interest to study whether intermittent CPAP usage will provide continued benefit in the treatment of OSA. When CPAP is discontinued, for a short period, the upper airway function may still remain normal. This may explain why some patients find intermittent use of their CPAP. It also opens up the possibility of reduction in CPAP pressure after using CPAP for a while. Caution must be exercised however, as there is limited information available regarding the onset and the maintenance period of such improvement. More studies are needed to address the incidence of the recurrence, the severity of obstructive events, and timing of symptom-free interval.

5.1. CPAP discontinuation studies

Kribbs et al. reported effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with OSA. Although the RDI of the CPAP night ($M = 36.8$, SD = 28.0 events/h) was significantly lower than the pretreatment baseline ($M = 56.6$, SD = 24.0 events/h), other subjective measures of sleepiness and fatigue and objective measures of Stanford sleepiness scale (SSS), multiple sleep latency test (MSLT), and psychomotor vigilance task (PVT) reversed to abnormal values after one night without CPAP treatment [101].

In a study of OSA patients treated with CPAP ($n = 22$), long-term effects of CPAP were reviewed. Patients had no significant weight changes but required lower level of CPAP pressure. This was attributed to the reduction in pharyngeal mucosal edema and altered upper airway muscle dynamics [102]. In another prospective, controlled, single-blind crossover study, Jokic and colleagues demonstrated that CPAP level requirements fell (median difference 1.5 cm H_2O, CI 1.1–2.7 cm H_2O, $P = 0.0004$) within 2 weeks of starting CPAP [103].

When CPAP was discontinued in OSA patients for 2 weeks in a randomized controlled trial by Yang et al., although the markers of the systemic inflammation remained unchanged, the sympathetic activity increased. Despite recurrence of sleepiness and impaired vigilance, the neurobehavioral and performance tests were unaffected by the CPAP withdrawal [104].

6. Conclusion

This review emphasizes the importance of reversibility of anatomic and physiologic processes that contribute to the etiology of OSA. It further brings into question issues related to compliance and highlights the possibility of more research into longitudinal sustainability of changes that occur after the currently available treatment options.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.01.002.

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